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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,905	07/25/2003	Guido Franzoso	21459-94575	2235

7590 08/04/2008

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EXAMINER	
AEDER, SEAN E	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
08/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,905	FRANZOSO ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/1/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-37* is/are pending in the application.

4a) Of the above claim(s) *3-5,7-35 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/22/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 5/1/08 in response to the Office Action of 11/1/07 are acknowledged and have been entered.

Claims 1 and 3-37 are pending.

Claims 3-5, 7-35, and 37 have been withdrawn.

Claims 1 and 6 have been amended by Applicant.

Claims 1, 6, and 36 are currently under examination.

The following Office Action contains NEW GROUNDS of rejections necessitated by New Considerations.

Rejections Withdrawn

The rejection under 35 U.S.C. 112, second paragraph, is withdrawn.

The rejection under 35 U.S.C. 112 first paragraph, for failing to comply with the written description requirement, is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, and 36 remain rejected under 35 U.S.C. 112 first paragraph, for failing to comply with the enablement requirement, for the reasons stated in the Office Actions of 3/30/06, 11/29/06, 11/1/07, and for the reasons set-forth below.

While being enabling for an *in vitro* method for increasing JNK activation leading to programmed cell death comprising selecting an agent comprising a cell-permeable peptide comprising amino acids 132-156 of SEQ ID NO:50 wherein said peptide blocks suppression of JNK activation by Gadd45β and treating cultured cells with said agent to increase programmed cell death of said cultured cells, does not reasonably provide enablement for *in vivo* methods for increasing JNK activation leading to programmed cell death comprising selecting an agent that blocks suppression of JNK activation by Gadd45β and using said agent to increase programmed cell death.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method for modulating a JNK pathway leading to programmed cell death. The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant

Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are drawn to a method for modulating a JNK pathway leading to programmed cell death comprising selecting a peptide comprising an amino acid sequence within the kinase domain of JNKK2 that blocks suppression of JNK activation by Gadd45b; and contacting a cells with the peptide to increase programmed cell death due to activation of JNKK2. The claims encompass in vitro and in vivo modulation of a JNK pathway.

Quantity of experimentation

The quantity of experimentation required to perform the claimed invention in vivo is extremely large. It would require significant study to determine which, if any, of the peptides capable of modulating JNK pathway in vitro are in fact capable of modulating JNK pathway in vivo. Further, it would require significant study to determine which cells in vivo may be susceptible to programmed cell death upon contacting said peptides. Further, it would require significant study to determine how to direct said peptides to said cells. The identification and characterization of the peptides capable of vivo modulating JNK pathway would be inventive, unpredictable, and difficult, requiring years of inventive effort with no guarantee of success in doing so.

Working examples

The specification teaches that Gadd45β binds to JNKK2, blocks JNK activation and prevents apoptosis in vitro (see Fig. 22A). The specification teaches Gadd45 is a physiologic target of NFkB in vitro (Example 2) and Gadd45β effectively blocks

apoptotic pathways in NFkB null cells. The specification teaches Gadd45β is a specific inhibitor of JNK activation in vitro. Moreover specification teaches a method for screening for agents that bind Gadd45β, or prevent the ability of Gadd45β to block apoptosis, or prevent the ability of Gadd45V to block JNK activation in vitro (see page 65, last paragraph, page 66, last paragraph and page 67,2nd paragraph). However, the specification fails to show that a modulator for the interaction of Gadd45β and JNKKs modulates JNK pathway, and thereby, apoptosis in vivo.

Guidance in the specification

The specification provides insufficient guidance and objective evidence to indicate to one of skill in the art that the administration of a peptide comprising an amino acid sequence within the kinase domain of Gadd45β would modulate JNK pathway and programmed cell death in vivo.

The unpredictability of the art and the state of the prior art

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening possible effects of compounds in vivo. However, in vivo correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to in vivo response with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a response to a compound. Furthermore it is well

known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment.

Level of skill in the art

The level of skill in the art is deemed to be high.

Declaration by Guido Franzoso

A Declaration under 37 CFR 1.132 was submitted on 8/30/06 by Guido Franzoso. Said Declaration states that Gadd45β modulates JNKK2 activity *in vivo*, in a mouse model (see paragraph 9 of the Declaration, in particular). The Declaration states that Gadd45β knock-out mice do not have functional Gadd45β and therefore cannot modulate JNK activity and JNK activation leads to cell death in mice following hepatectomy (see paragraph 10 of the Declaration, in particular). The Declaration states that the data from Gadd45β knock-out mice model and JNK2 knock-out mice model provides evidence that Gadd45β is a modulator of JNK pathway in regulating cell death *in vivo* (see page 4 of the Declaration, in particular). The Declaration indicatates that the mouse model further supports the results obtain earlier from cell culture and *in vitro* studies in the specification that demonstrated reasonable correlation to *in vivo* efficacy established by the interaction and modulation of JNK pathway (see paragraph 18 of the Declaration, in particular).

While the data presented in the Declaration demonstrate that Gadd45β gene regulates JNK activity and liver apoptosis, this is different from the claimed invention, which are directed to a method for modulating a JNK pathway leading to programmed cell death comprising selecting a peptide comprising an amino acid sequence within the kinase domain of JNKK2 that blocks suppression of JNK activation by Gadd45b; and contacting a cells with the peptide to increase programmed cell death due to activation

of JNKK2. The Declaration does not provide any data or evidence indicating that a peptide comprising an amino acid sequence within the kinase domain of JNKK2 that blocks suppression of JNK activation by Gadd45b, when administered to a subject, would induce programmed cell death *in vivo*. Further, even if were one to discover such a peptide that would inducle programmed cell death to a particular cell type in vivo, one of skill would be faced with overcoming problems related to delivering an effective concentration of said peptide to a target cell to which it induces programmed cell death, such that Gadd45b suppression of JNK activtion is blocked.

Conclusion

Given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

In the Reply of 5/1/08, Applicant argues that the examiner has not provided evidence to dispute Applicant representation that the in vitro data provides adequate correlation to in vivo effects. Applicant argues that the in vitro models used are standard and have been shown to reasonably correlate to in vivo effects. Applicant further argues that showing that Gadd45b binds to an inhibits JNKK2 in vitro, thereby removing a barrier to apoptosis, coupled with evidence that the absence of Gadd45b in

vivo removes a barrier to apoptosis, is sufficient to support the pending claims. Applicant further argues that the pending claims require programmed cell death and do not require a therapeutic or disease benefit. Applicant indicates that it is predictable that cells would die in vivo by performing the claimed method because it is possible to increase programmed cell death by treating cells in vitro with peptides encompassed by the claimed method.

The amendments to the claims and the arguments found in the Reply of 5/1/08 have been carefully considered, but are not deemed persuasive. In regards to the arguments that the examiner has not provided evidence to dispute Applicant representation that the in vitro data provides adequate correlation to in vivo effects and that the in vitro models used are standard and have been shown to reasonably correlate to in vivo effects, references that teach in vitro data is unpredictable for in vivo results have been presented above (see discussion of Freshney and Dermer, in particular). The instant specification provides no working examples that would indicate to one of skill in the art that administration of peptides encompassed by the claims would increase programmed cell death due to activation of JNKK2 in vivo. No specific animal model is disclosed in the specification to support such in vivo effect. Further, those of ordinary skill in the art recognize that in vivo effects of administered compounds are not predictive. The instant situation is analogous to that of *In re* Brana (34 U.S.P.Q. 2d 1436, 1440 (Fed. Cir. 1995)). A review of *In re Brana* reveals an application that claimed a chemical compound for treating a cancer, wherein the chemical compound was structurally similar to known compounds that have known in vivo use to treat

tumors, and more importantly, Applicant provided in vivo data that the claimed compound could treat tumors in mice, hence it was ruled that the claimed compound was enabled for treating tumors. In the instant application, the claims are not drawn to administering a product which has known in vivo ability to give rise to an increase in programmed cell death in vivo. Further, the instant specification provides no in vivo data, particularly demonstrating that administering peptides comprising an amino acid sequence within the kinase domain of JNKK2 would predictably give rise to a programmed cell death in vivo. In view of *In re Brana*, Examiner asserts that successful use of in vivo mouse models wherein peptides comprising an amino acid sequence within the kinase domain of JNKK2 are administered and induce programmed cell death in vivo enables methods of inducing programmed cell death in humans and does not require human clinical testing; however, the instant application is claiming method that induces an in vivo response upon administering a compound without providing any in vivo data comprising administering said compound, hence the claimed invention is not enabled. All of this underscores the criticality of providing workable examples which are not disclosed in the specification, particularly in an unpredictable art, such as in vivo treatments.

In regards to the argument that showing that Gadd45b binds to an inhibits JNKK2 in vitro, thereby removing a barrier to apoptosis, coupled with evidence that the absence of Gadd45b in vivo removes a barrier to apoptosis, is sufficient to support the pending claims, reasons why in vitro cell culture results do not predict in vivo results are discussed above. In regards to evidence that the absence of Gadd45b in vivo removes

a barrier to apoptosis, the presented in vivo data only demonstrates that Gadd45β gene regulates JNK activity and liver apoptosis. However, this is different from the claimed invention, which is directed to a method of *in vivo* modulating a JNK pathway and increasing programmed cell death due to activation of JNKK2 upon administration of one of a genus of peptides. The Declaration does not provide any data or evidence indicating that a peptide comprising an amino acid sequence within the kinase domain of JNKK2, when administered to a subject, would induce programmed cell death *in vivo*. Further, even if were one to discover such a peptide that would inducle programmed cell death to a particular cell type in vivo, one of skill would be faced with overcoming problems related to delivering an effective concentration of said peptide to a target cell to which it induces programmed cell death, such that Gadd45b suppression of JNK activtion is blocked.

It is acknowledged that the pending claims require programmed cell death and do not require a therapeutic or disease benefit.

In regards to the argument that it is predictable that cells would die in vivo by performing the claimed method because it is possible to increase programmed cell death by treating cells in vitro with peptides encompassed by the claimed method, reasons why in vitro cell culture data does not predict in vivo results are discussed above.

Double Patenting

Claim 1 and 6 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 6 of copending Application No. 10/623330 for the reasons stated in the Office Action of 8/30/06. Applicant has indicated that a terminal disclaimer over 10/263330 will be filed if the pending claims are allowable.

New Rejections Necessitated by New Considerations

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 60/328,811 and 60/326,492, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications 60/326,492 and 60/328,811 upon which priority is claimed fails to provide adequate support under the first paragraph of 35 U.S.C. 112 for claims 1, 6, and 36 of this application. Claims 1, 6, and 36 recite methods of selecting a peptide comprising an amino acid sequence within the kinase domain of JNKK2 that blocks suppression of JNK activation by Gadd45b; and contacting a cell with the peptide to increase programmed cell death. The provisional application no: 60/326,492 does not mention JNKK2. While the provisional application 60/328,811 discloses JNKK2 (see specification page 6, line 12, page 8, line 29, page 14, line 5 and page 45, line 22), there is no disclosure of methods of selecting a peptide comprising an amino acid sequence within the kinase domain of JNKK2 that blocks suppression of JNK activation by Gadd45b; and contacting a cell with the peptide to increase programmed cell death. Accordingly, the claims 1, 6, and 36 have been determined to have the filing date of parent case 10/263330 (10/2/02).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Reinhard et al (US 6,492,112; 12/10/02).

Reinhard et al. teaches a method of inducing apoptosis of a cell comprising contacting cell with JNKK2 polypeptides (referred to by Reinhard et al as MKK7), which are capable of phosphorylating a JNK substrate (see column 18, lines 54-57) and would comprise an amino acid sequence within the kinase domain of JNKK2 required to phosphorylate a JNK substrate. Reinhard et al. further teaches a method of inducing apoptosis of a cell by treating with a JNKK2 polypeptide (see column 2, last paragraph). Reinhard et al. further teaches that these polypeptides which would modulate signal transduction through a JNK pathway would be used to enhance or decrease cellular responses to stress mediated through the JNK pathway (see column 19, lines 46-49).

Although Reinhard et al. does not explicitly teach that these peptide block suppression of JNK activation by Gadd45b and interfere with the interaction of Gadd45β and JNKK2, blocking suppression of JNK activation by Gadd45b and interfering with the interaction of Gadd45β and JNKK2 is considered an inherent property of these polypeptides. This is because the binding complex of Gadd45β and JNKK2 exists naturally in stressed cells and can be isolated from natural source, as evidenced by Papa et al. (Nature Cell Biology, 2004, 6(2), 146-153) where Papa et al. shows the interaction between endogenous Gadd45β and MKK7 (JNKK2) was detected readily by immunoprecipitation using an-Gadd45β antibodies (see page147, lines 2-6) and that said interaction blocks MKK7 activity (see abstract). Further, the polypeptides used in the method of Reinhard et al are taught to satisfy all the structural requirements recited

in the instant claims. Further, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Examiner, Art Unit 1642